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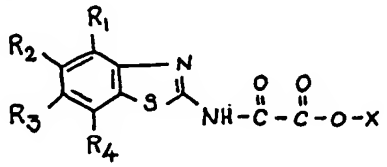
(19)

(54) NEW N-(BENZTHIAZOL-2-YL)-OXAMIC ACID DERIVATIVES AND THE PREPARATION THEREOF

(71) We, BOEHRINGER MANNHEIM G.M.B.H., of Mannheim-Waldhof, Federal Republic of Germany, a Body Corporate organised under the laws of the Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new N - (benzthiazol - 2 - yl) - oxamic acid derivatives and with the preparation thereof.

The new N - (benzthiazol - 2 - yl) - oxamic acid derivatives according to the present invention are compounds of the general formula:—



(I)

wherein R_1, R_2, R_3 and R_4, which can be the same or different, are hydrogen or halogen atoms, hydroxyl or nitro groups, phenyl radicals, straight-chained or branched lower alkyl or alkoxy radicals or trifluoromethyl radicals or R_2 and R_3 can together also represent a methylenedioxy radical and X is a hydrogen atom or a lower alkyl radical, with the proviso that when X is an ethyl radical, R_1, R_2, R_3 and R_4 cannot all be hydrogen atoms; and the pharmacologically acceptable salts of those compounds in which X is a hydrogen atom.

The lower alkyl and lower alkoxy radicals in the case of substituents R_1, R_2, R_3, R_4 and X are radicals containing up to 6 and preferably up to 4 carbon atoms. In the particular case of X, the lower alkyl radical is preferably an ethyl radical. The lower, straight-chained or branched alkyl radicals of the substituents R_1, R_2, R_3 and R_4 are preferably methyl, ethyl, *n* - propyl, isopropyl or *tert.* - butyl radicals.

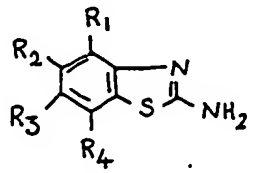
The halogen atom is fluorine, chlorine or bromine, chlorine being preferred.

We have found that the new compounds of general formula (I) according to the present invention display, when administered parenterally and also orally, an outstanding anti-allergic action, which can be demonstrated pharmacologically in the passive cutaneous anaphylactic (PCA test) *in vivo* in rats. The inhibition potency of these new compounds can also be convincingly demonstrated *in vitro* by antigen-induced mast cell degranulation.

The unsubstituted representative of compounds of general formula (I), namely, ethyl N - (benzthiazol - 2 - yl) - oxamate, is known from the literature (cf. P. A. Petjunin, Zh. Obshch. Khim., *34*(1), 28—32/1964). However, no therapeutic use of effectiveness is mentioned for this ethyl ester, mention only being made of its use as an intermediate for the preparation of N - (benzthiazol - 2 - yl) - oxamic acid hydrazide, which is an antituberculosis agent.

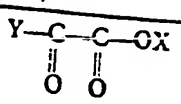
Therefore, the new compounds of general formula (I) according to the present invention are also valuable intermediates for the synthesis of pharmaceutically useful compounds, for example, new N - (benzthiazol - 2 - yl) - oxamic acid hydrazides with an antituberculosis action.

The new compounds according to the present invention can be prepared, for example, by reacting a 2 - aminothiazole compound of the general formula:—



(II)

wherein R_1, R_2, R_3 and R_4 have the same meanings as above, with an oxalic acid derivative of the general formula:—



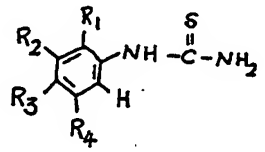
(III)

wherein X has the same meaning as above and Y is a lower alkoxy radical or a halogen atom, or with a salt of such an oxalic acid derivative, the resulting oxamic acid derivative of general formula (I), in which X is a hydrogen atom or a lower alkyl radical, or a salt thereof as intermediate can, if desired, be converted into another compound of general formula (I) by known methods of esterification or saponification, whereas free carboxylic acids of general formula (I), in which X is a hydrogen atom, can, in a special variant of the process, also be obtained thermolytically from the *tert.* - butyl ester.

Furthermore, it is possible to convert oxamates of general formula (I), wherein R_1, R_2, R_3 or R_4 are hydroxyl groups or alkoxy radicals, into one another by etherification or ether splitting, whereby, at the same time, a transesterification or saponification can take place in the course of this reaction.

Some of the 2 - aminobenzthiazoles of general formula (II) used as starting material are new and can be prepared by ring closure reactions known from the literature, preferably by one of the following methods:

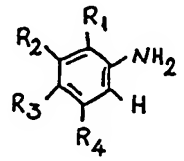
a) by the Hugershoff reaction:
in which a thiourea of the general formula:—



(IV)

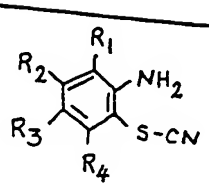
wherein R_1, R_2, R_3 and R_4 have the same meanings as above, is cyclised with dehydrogenation with bromine in an appropriate solvent, for example chloroform, with the formation of a compound (II); or

b) by the Kaufmann method:
in which an aniline derivative of the general formula:—



(V)

wherein R_1, R_2, R_3 and R_4 have the same meanings as above, is thiocyanated in the *o*-position and, possibly without isolation of the intermediate thiocyano compound of the general formula:—



(VI)

wherein R_1, R_2, R_3 and R_4 have the same meanings as above, cyclised to give a 2 - aminobenzthiazole of general formula (II).

Some of the thioureas of general formula (IV) required as intermediates are also new and can be prepared by methods known from the literature from the above-mentioned aniline derivatives of general formula (V), as described hereinafter in the Examples (see also Org. Synth. Coll. Vol. III, 735/1955).

The reaction of compounds of general formula (II) with oxalic acid ester halides of general formula (III), especially oxalic acid ethyl ester chloride, takes place in aprotic solvents, such as methylene chloride, pyridine, chloroform or carbon tetrachloride, at ambient temperature (Method A). The reaction of 2-amino compounds of general formula (II) with oxalic acid dialkyl esters, such as diethyl oxalate and ethyl *tert.* - butyl oxalate, preferably takes place without the use of a solvent under reflux or at a temperature of up to about 150°C. (Method B). When using ethyl *tert.* - butyl oxalate, the oxamic acid derivatives are obtained directly since, according to Method B, 2 - methylprop - 1 - ene is thermolytically split off under the reaction conditions.

A conversion of substituents R_1, R_2, R_3, R_4 and X which is possibly to be carried out subsequently to the condensation can be carried out according to known methods. Thus, for example, a compound of general formula (I), in which R_1 is, for example, a hydroxyl group, can be converted into an alkoxy group by means of appropriate alkylation agents. On the other hand, alkoxy radicals can be converted into hydroxyl groups by conventional methods. Furthermore, carboxylic acid esters of general formula (I) (X=alkyl) can be saponified to the corresponding free carboxylic acids (X=hydrogen) with the use of mineral acids or of alkali metal hydroxides in a polar solvent, such as water, methanol, ethanol, dioxan or acetone. The saponification is advantageously carried out with the use of a strong base, such as sodium or potassium hydroxide, in a mixture of methanol and water at ambient temperature or at a moderately elevated temperature. On the other hand, however, the carboxylic acids can be esterified in conventional manner or esters with a particular radical X can be converted into esters with a different radical X by transesterification. The esterification of the carboxylic acids is preferably carried out in the presence of an acidic catalyst, for example hydrogen chloride, sulphuric acid or *p* -

toluenesulphonic acid, or of a strongly acidic ion exchange resin. Transesterifications, on the other hand, require the addition of a small amount of a basic substance, for example of an alkali metal or alkaline earth metal hydroxide or of an alkali metal alcoholate.

For the preparation of salts with pharmacologically acceptable organic or inorganic bases, for example sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, methylglucamine, morpholine or ethanolamine, the carboxylic acids can be reacted with appropriate bases. Mixtures of the carboxylic acids with an appropriate alkali metal carbonate or bicarbonate can also be used.

For the preparation of pharmaceutical compositions, at least one compound of general formula (I) is mixed in the usual manner with appropriate pharmaceutical carriers or diluents, and optionally with aroma, flavouring and colouring materials and formed, for example, into tablets or dragees, or, with the addition of appropriate adjuvants, suspended or dissolved in water or an oil, for example olive oil.

The compounds of general formula (I) can be administered orally or parenterally in liquid or solid form. As injection medium, it is preferable to use water which contains the stabilising agents, solubilising agents and/or buffers usual for injection solutions. Additives of this type include, for example, tartrate or borate buffers, ethanol, dimethyl sulphoxide, complex forming agents (such as ethylenediamine - tetraacetic acid), high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation or polyethylene derivatives of sorbitan anhydrides.

Solid carrier materials which can be used include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acid, high molecular weight fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycols). Compositions suitable for oral administration can, if desired, contain flavouring and/or sweetening materials. For external use, the compounds of general formula (I) can also be used in the form of powders and salves; for this purpose, they are mixed, for example, with powdered, physiologically acceptable diluents or with conventional salve bases.

The following Examples are given for the purpose of illustrating the present invention. The structures of the compounds referred to in these Examples was verified by CHN analyses and IR, UV, NMR and mass spectra. Of the total analyses, in the individual Examples characteristic individual determinations of physical data are given.

Example 1

Ethyl N - (4 - methoxybenzthiazol - 2-yl) - oxamate.

Method A:

18.02 g. (0.1 mol) 2 - Amino - 4 - methoxybenzthiazole are dissolved in 250 ml. methylene chloride, with the addition of 16.1 ml. pyridine, and mixed within the course of 15 minutes, at a temperature of 8—10°C., with a solution of 15.01 g. (12.3 ml.; 0.11 mol) oxalic acid ethyl ester chloride in 30 ml. methylene chloride. The reaction mixture is subsequently further stirred for 20 minutes at 10°C., the precipitate formed is then filtered off and the filtrate is evaporated in a vacuum. The evaporation residue is then stirred with approximately 0.5N hydrochloric acid and the solid material filtered off with suction. It is then washed with dilute hydrochloric acid and water, dried (crude yield 27.8 g.; m.p. 173—174°C.) and recrystallised from nitromethane. There are obtained 24.8 g. ethyl N - (4 - methoxybenzthiazol - 2 - yl) - oxamate. Yield 88.47% of theory. The structure is verified by CHN analysis, IR, UV, NMR and mass spectra (M.W. 280).

Method B:

18.02 g. (0.1 mol) 2 - Amino - 4 - methoxybenzthiazole are heated under reflux for 4 hours in 135 ml. diethyl oxalate. The reaction mixture is then hot filtered, cooled and the precipitate thereby obtained filtered off with suction, washed with cold ethanol and recrystallised from nitromethane. There are thus obtained 18.1 g. (64.6% of theory) ethyl N - (4 - methoxybenzthiazol - 2 - yl) - oxamate; m.p. 175°C. The IR spectrum shows that the product obtained is identical with that obtained according to Method A (*inter alia* carbonyl bands at 1705 cm^{-1} (5.87 μ) and 1740 cm^{-1} (5.75 μ)).

Example 2

N - (4 - Methoxybenzthiazol - 2 - yl) - oxamic acid and the sodium salt thereof.

Method A:

a) 5 g. (0.0178 mol) of the ethyl ester obtained according to Example 1 are suspended in 150 ml. water and mixed within the course of 45 minutes, at ambient temperature, with 17.8 ml. 1N aqueous sodium hydroxide solution. After stirring for 2 hours, the reaction mixture is filtered and the desired sodium salt obtained as a crude product by freeze drying. Thereafter, the salt is taken up in 100 ml. water, again filtered and the desired acid liberated by the addition of 2N hydrochloric acid. After drying, there are obtained 3.05 g. (68% of theory) of N - (4 - methoxybenzthiazol - 2 - yl) - oxamic acid; m.p. 223—225°C.

b) 1.2 g. of the acid obtained according to Example 2a) are suspended in 100 ml. water and neutralised with 4.75 ml. 1N aqueous sodium hydroxide solution. The clear solution thus obtained is then freeze dried. There is obtained 1.21 g. sodium N - (4 - methoxybenzthiazol - 2 - yl) - oxamate with a water content of 8% by weight; m.p. 255—256°C. (decomp.).

Method B:

5 g. (0.0277 mol) 2 - Amino - 4 - methoxybenzthiazole are heated for 2 hours at 150°C. with 24.13 g. ethyl *tert.* - butyl oxalate. After cooling, the reaction mixture is diluted with diethyl ether and suction filtered. The solid product is then washed with diethyl ether to give 6.17 g. of a compound melting at 221—223°C. which, according, *inter alia*, to the IR spectrum, is identical with the N - (4 - methoxybenzthiazol - 2 - yl) - oxamic acid prepared according to Example 2, Method A. Yield 88.3% of theory; mass spectrum found M.W. 252.

Example 3

Ethyl N - (6 - methoxybenzthiazol - 2 - yl) - oxamate.

18 g. (0.1 mol) 2 - Amino - 6 - methoxybenzthiazole are reacted with 15.01 g. (0.11 mol) oxalic acid ethyl ester chloride in 280 ml. methylene chloride in the presence of 16 ml. pyridine in the manner described in Example 1, Method A. The precipitate obtained is filtered off with suction and washed with dilute hydrochloric acid and water. After recrystallisation from ethyl acetate, there are obtained 9.1 g. of substance melting at 193—194°C. The first filtrate is evaporated in a vacuum, the residue is stirred with diethyl ether and the solid product is filtered off with suction. It is washed with dilute hydrochloric acid and water and subsequently recrystallised from ethyl acetate, with the addition of active charcoal. There are obtained a further 11.7 g. of compound with a melting point of 192°C. The total yield of the desired ethyl N - (6 - methoxybenzthiazol - 2 - yl) - oxamate is thus 20.8 g. (74.20% of theory). IR Spectrum: 1730 cm^{-1} (5.78 μ), 1710 cm^{-1} (5.84 μ) for the carbonyl bands; 3270 cm^{-1} (3.06 μ) for the NH band. Mass spectrum: M.W. 280.

Example 4

N - (6 - Methoxybenzthiazol - 2 - yl) - oxamic acid.

According to Example 2, Method A, 5 g. (0.0178 mol) of the ethyl oxamate obtained according to Example 3 are suspended in 150 ml. water and, after the addition of 17.8 ml. 1N aqueous sodium hydroxide solution, saponified by stirring for 2 hours at ambient temperature. The reaction mixture is filtered and the sodium salt of N - (6 - methoxybenzthiazol - 2 - yl) - oxamic acid isolated by freeze drying. Yield 4.1 g. (84.01% of theory); m.p. >300°C.

2 g. of this sodium salt are dissolved in 50 ml. water and the clear solution obtained acidified with 2N hydrochloric acid to a pH value of 2. The yellow precipitate obtained is filtered off with suction, then washed with water and dried in a vacuum at 50°C. There are obtained 1.4 g. of the free N - (6 - methoxybenzthiazol - 2 - yl) - oxamic acid; m.p. 227—228°C. The structure was determined *inter alia* by the nuclear resonance spectrum. Mass Spectrum: found M.W. 252.

Example 5

Ethyl N - (6 - ethoxybenzthiazol - 2 - yl) - oxamate.

According to Example 1, Method A, 5.8 g. (0.03 mol) 2 - amino - 6 - ethoxybenzthiazole and 4.5 g. (0.033 mol) oxalic acid ethyl ester chloride in 85 ml. methylene chloride are reacted within the course of 1 hour, with the addition of 4.83 ml. pyridine. There are obtained 6.7 g. (76% of theory) ethyl N - (6 - ethoxybenzthiazol - 2 - yl) - oxamate, which melts at 183—184°C. after recrystallisation from nitromethane. Mass Spectrum: found M.W. 294. Thin layer chromatogram: chloroform : methanol 9 : 1.

Example 6

Ethyl N - (5 - methoxybenzthiazol - 2 - yl) - oxamate.

Analogously to Example 1, Method A, 18.02 g. (0.1 mol) 2 - amino - 5 - methoxybenzthiazole are reacted with 15.01 g. (0.11 mol) oxalic acid ethyl ester chloride, with the addition of 16.1 ml. pyridine, in 280 ml. methylene chloride during a total reaction time of 35 minutes at 10°C. Subsequently the product formed is filtered off with suction, washed with 2N hydrochloric acid and water and the crude product (26.4 g.; 94.2% of theory; m.p. 165—166°C.) recrystallised from nitromethane. There are obtained 22.9 g. (81.7% of theory) ethyl N - (5 - methoxybenzthiazol - 2 - yl) - oxamate; m.p. 168—169°C. The molecular weight was found to be 280. IR: 1738 cm^{-1} (5.77 μ), 1698 cm^{-1} (5.89 μ) for carbonyl bands, 3265 cm^{-1} (3.06 μ) for the NH band.

Example 7

N - (5 - Methoxybenzthiazol - 2 - yl) - oxamic acid and the sodium salt thereof.

5 g. (0.0178 mol) of the ester described in Example 6 are, according to Example 2a) and b), Method A, suspended in 150 ml. water and saponified by the addition of 17.8 ml. aqueous sodium hydroxide solution within the course of 2 hours at ambient temperature. After filtration, the aqueous solution is freeze dried. There are obtained 3.4 g. sodium N - (5 - methoxybenzthiazol - 2 - yl) -

oxamate (69.7% of theory); m.p. 329°C.; water content 5% by weight.

A sample of the sodium salt is dissolved in water and mixed with 1N hydrochloric acid. In this manner, the acid is isolated in analytically pure form and has a melting point of 228—229°C.

Example 8

Ethyl N - (7 - isopropyl - 4 - methoxybenzthiazol - 2 - yl) - oxamate.

a) 7.03 g. (0.05 mol) benzoyl chloride are dissolved in 25 ml. acetone and mixed at 15—20°C. with a solution of 3.8 g. (0.05 mol) ammonium thiocyanate in 25 ml. acetone. To this solution there is added dropwise, within the course of 10 minutes, a solution of 8.26 g. (0.05 mol) 2 - amino - 4 - isopropyl - anisole in 25 ml. acetone. The reaction mixture is heated under reflux for 4.5 hours and then poured on to ice. By suction filtration there is obtained, as intermediate product, 1 - (5 - isopropyl - 2 - methoxyphenyl) - 3 - benzoylurea which, according to the thin layer chromatogram, is sufficiently pure for further working up.

b) The N - benzoylurea derivative prepared according to Example 8a) is suspended in 150 ml. methanol and mixed with 4 g. sodium methylate. Dissolving takes place at once and the reaction mixture is then stirred for 1 hour at ambient temperature, thereafter mixed with 2N hydrochloric acid until the pH is 4—4.5, evaporated in a vacuum and the oily residue triturated with ligroin. The solid product is filtered off with suction, washed with water and dried in a vacuum at 70°C. In this way, there is obtained 1 - (5 - isopropyl - 2 - methoxyphenyl) - thiourea; m.p. 109—111°C. The yield is 8.1 g. (72.25% of theory, referred to the 2 - amino - 4 - isopropylanisole).

c) The thiourea derivative is then ring closed by Hugershoff's method to give a substituted 2 - aminobenzthiazole:

7.85 g. (0.035 mol) of the substituted phenylthiourea prepared according to Example 8b) are dissolved in 70 ml. chloroform and mixed at 20—30°C. within the course of 5 minutes with a solution of 5.7 g. (0.0357 mol) bromine in 10 ml. chloroform. The reaction mixture is heated under reflux for 45 minutes, a vigorous evolution of hydrogen bromide taking place. It is then allowed to cool and the precipitate obtained is filtered off with suction and stirred first with a solution of sodium hydrogen sulphite and subsequently with a 2N aqueous solution of sodium hydroxide. The precipitate is again collected, washed with water and dried in a vacuum. There are obtained 6.4 g. (82.26% of theory) 2 - amino - 7 - isopropyl - 4 - methoxybenzthiazole; m.p. 189—191°C.

d) For the preparation of the oxamate, 4.45 g. (0.02 mol) of the 2 - aminobenzthiazole prepared according to Example 8c) are reacted according to Example 1. Method A with 2.99 g. (0.022 mol) oxalic acid ethyl ester chloride in 60 ml. methylene chloride, with the addition of 3.2 ml. pyridine. After working up the reaction mixture in an analogous manner, from the crude product there are obtained, by recrystallisation from ethanol, with the addition of active charcoal, 4.6 g. (71.31% of theory) ethyl N - (7 - isopropyl - 4 - methoxy - benzthiazol - 2 - yl) - oxamate; m.p. 180—181°C. Mass spectrum: molecular weight found: 322.

Example 9

Ethyl N - (4 - methoxy - 7 - phenylbenzthiazol - 2 - yl) - oxamate.

a) According to Example 8a), from 9.96 g. (0.05 mol) 2 - amino - 4 - phenylanisole, 3.8 g. (0.05 mol) ammonium thiocyanate and 5.8 ml. (0.05 mol) benzoyl chloride in 50 ml. acetone, there is obtained, as crude product, a practically quantitative yield of 1 - [(2 - methoxy - 5 - phenyl) - phenyl] - 3 - benzoylthiourea; m.p. 138—142°C.

b) Analogously to Example 8b), from the N - benzoyl compound prepared according to Example 9a), by the addition of sodium methylate to a methanolic suspension thereof, there are obtained 10.68 g. (82.79% of theory, referred to the anisole derivative used) 1 - [(2 - methoxy - 5 - phenyl) - phenyl] - thiourea; m.p. 190—192°C.

c) Analogously to Example 8c), according to the Hugershoff method, there are obtained from 8 g. (0.031 mol) of the thiourea prepared according to Example 9b), with 1.98 ml. (0.0388 mol) bromine in 75 ml. chloroform, 7.17 g. of a solid product with a melting point of 187—190°C. This is an addition compound of 2 - amino - 4 - methoxy - 7 - phenylbenzthiazole hydrobromide with 1 ml. of the free base. By subsequent treatment with an aqueous solution of sodium bicarbonate, there remain behind 5.82 g. of the desired substituted 2 - aminobenzthiazole; m.p. 202—204°C. Yield 73% of theory.

d) The reaction to give the oxamate is carried out according to Example 8d). From 5.8 g. (0.0226 mol) of the 2 - aminobenzthiazole prepared according to Example 9c), there are obtained, with 3.95 ml. oxalic acid ethyl ester chloride in 90 ml. methylene chloride and 5 ml. pyridine, 7.45 g. (92.38% of theory) ethyl N - (4 - methoxy - 7 - phenylbenzthiazol - 2 - yl) - oxamate; m.p. 183—185°C. Molecular weight found 356. Further analysis, including the nuclear resonance spectrum, confirmed the structure of the product.

Example 10

Ethyl N - (7 - *tert.* - butyl - 4 - methoxybenzthiazol - 2 - yl) - oxamate.

The preparation is carried out in the manner described in Examples 8a)—d):

a) 1 - (5 - *tert.* - butyl - 2 - methoxyphenyl) - 3 - benzoylthiourea is obtained from 2 - amino - 4 - *tert.* - butylanisole, ammonium thiocyanate and benzoyl chloride in almost quantitative crude yield: m.p. 160—162°C.

b) 1 - (5 - *tert.* - Butyl - 2 - methoxyphenyl) - thiourea is obtained by the alkaline debenzoylation of the benzoylthiourea described in Example 10a) with dilute aqueous sodium hydroxide solution or methanolic sodium methylate solution in 75% yield, referred to the anisole derivative used; m.p. 166—167°C.

c) By means of the Hugershoff reaction, according to Example 8c), there are obtained from 4.76 g. (0.02 mol) of the phenylthiourea prepared according to Example 9b) with 3.27 g. (0.0204 mol) bromine in 40 ml. chloroform, 4.1 g. (86.86% of theory) 2 - amino - 7 - *tert.* - butyl - 4 - methoxybenzthiazole; m.p. 225—226°C.

d) Analogously to Example 1 Method A, 3.54 g. (0.015 mol) of the 2 - aminobenzthiazole prepared according to Example 10c) are reacted with 2.25 g. oxalic acid ethyl ester chloride in 45 ml. methylene chloride and 2.4 ml. pyridine. After recrystallisation of the crude product obtained from ethanol, there are obtained 3.5 g. (69.44% of theory) ethyl N - (7 - tert. - butyl - 4 - methoxybenzthiazol - 2 - yl) - oxamate; m.p. 181—182°C.

Mass spectrum: molecular weight found 336.

UV (methanol): 308 mμ log ε 4.04.

Example 11

Ethyl N - (4,7 - dimethoxybenzthiazol - 2 - yl) - oxamate.

The preparation takes place according to the procedure described in Example 8a)—d):

a) 1 - (2,5 - Dimethoxyphenyl) - 3 - benzoylthiourea is obtained from 2,5 - dimethoxyaniline, benzoyl chloride and ammonium thiocyanate (mole ratio 1:1:1) in acetone. The crude product, obtained in practically quantitative yield, has a melting point of 140—144°C.

b) 1 - (2,5 - Dimethoxyphenyl) - thiourea is prepared from the crude product obtained according to Example 11a) by treatment with methanolic sodium methylate solution. From 15.1 g. (0.1 mol) 2,5 - dimethoxyaniline there are obtained 13.12 g. (61.9% of theory) of the desired thiourea; m.p. 160—162°C.

c) By the Hugershoff ring closure, from 12 g. (0.056 mol) of the thiourea prepared according to Example 11b), there are obtained, with bromine in chloroform, 9.41 g. (79.54% of theory) 2 - amino - 4,7 - dimethoxybenzthiazole; m.p. 210—213°C.

d) 7 g. (0.03 mol) of the aminobenzthiazole prepared according to Example 11c) are reacted with 4.78 ml. oxalic acid ethyl ester chloride in 100 ml. methylene chloride and 6.3 ml. pyridine. There are obtained 7.55 g. (81.1% of theory) ethyl N - (4,7 - dimethoxybenzthiazol - 2 - yl) - oxamate; m.p. 223—225°C.

Mass spectrum: molecular weight found: 310.

UV (methanol) λ_{max}: 308 mμ log ε 4.01.

Example 12

Ethyl N - (5,6 - dimethoxybenzthiazol - 2 - yl) - oxamate.

a) According to Example 8a) and b), from 100 g. 3,4 - dimethoxyaniline (0.65 mol), 94.2 g. benzoyl chloride (0.67 mol) and 49.7 g. ammonium thiocyanate in 620 ml. acetone, there are obtained 113.6 g. (83.31% of theory) 1 - (3,4 - dimethoxyphenyl) - thiourea which, after recrystallisation from ethanol, melts at 228—230°C.

b) By means of the Hugershoff method described in Example 8c), ring closure takes place with 106.13 g. (0.5 mol) of the thiourea prepared according to Example 12a) in 89.1% yield (93.7 g. after recrystallisation from ethanol), with the formation of 2 - amino - 5,6 - dimethoxybenzthiazole; m.p. 220—221°C.

c) According to the procedure described in Example 1, Method A, 6.3 g. (0.03 mol) of the aminobenzthiazole prepared according to Example 12b) are reacted with 4.3 ml. oxalic acid ethyl ester chloride in 100 ml. methylene chloride and 5.6 ml. pyridine to give 7.14 g. (76.7% of theory) ethyl N - (5,6 - dimethoxybenzthiazol - 2 - yl) - oxamate; m.p. 190—191°C. after recrystallisation from ethanol.

Mass spectrum: molecular weight found 310.

UV (methanol): λ_{max}: 331 mμ log ε 4.09.

Example 13

Ethyl N - (4,6 - dimethoxybenzthiazol - 2 - yl) - oxamate.

In a manner analogous to that described in Example 11 for the 4,7 - dimethoxy derivative and in Example 12 for the 5,6 - dimethoxy derivative, there is obtained, starting from 2,4 - dimethoxyaniline, ethyl N - (4,6 - dimethoxybenzthiazol - 2 - yl) - oxamate.

Example 14

Ethyl N - (6 - methoxy - 5,7 - dimethylbenzthiazol - 2 - yl) - oxamate.

The working conditions described in Example 8a)—d) are employed:

a) 1 - (4 - Methoxy - 3,5 - dimethylphenyl) - 3 - benzoylthiourea is obtained in practically quantitative yield from 4 - amino - 2,6 - dimethylanisole, ammonium thiocyanate and benzoyl chloride; m.p. of the crude product moistened with acetone: 118—120°C.

b) 1 - (4 - Methoxy - 3,5 - dimethylphenyl) - thiourea is obtained by debenzoylating the compound obtained according to Example 14a). Yield 81.35% of theory; m.p. 216—217°C.

c) 2 - Amino - 6 - methoxy - 5,7 - dimethylbenzthiazole is obtained by the Hugershoff ring closure of the thiourea obtained according to Example 14b) (e.g. batch size 8 g.=0.038 mol) in 65% yield; m.p. 191—193°C.

d) From 4.7 g. (0.0225 mol) of the aminobenzthiazole prepared according to Example 14c), there are obtained, by reaction with 3.2 ml. (0.0286 mol) oxalic acid ethyl ester chloride in 75 ml. methylene chloride and 4.1 ml. pyridine, 6.45 g. (93% of theory) ethyl N - (6 - methoxy - 5,7 - dimethylbenzthiazol - 2 - yl) - oxamate; m.p. 150—160°C.

Mass spectrum: molecular weight found 308.

UV spectrum: λ_{max}: 327 mμ log ε 4.09.

Example 15

Ethyl N - (4 - methoxy - 5,7 - dimethylbenzthiazol - 2 - yl) - oxamate.

a) Analogously to the procedure described in Example 8a) and b), there are obtained from 7.56 g. (0.05 mol) 2 - amino - 4,6 - dimethylanisole, benzoyl chloride and ammonium thiocyanate, without characterisation of the N - benzoyl intermediate, 8.1 g. 1 - (2 - methoxy - 3,5 - dimethylphenyl) - thiourea; yield 77% of theory; m.p. 141—142°C.

b) 7.36 g. (0.035 mol) of the substituted thiourea prepared according to Example 15a) is reacted, analogously to Example 8c), with bromine in chloroform to give 2 - amino - 4 - methoxy - 5,7 - dimethylbenzthiazole; yield 97.3% of theory (7.1 g.); m.p. 164—166°C.

c) 4.16 g. (0.02 mol) of the aminobenzthiazole prepared according to Example 15b) are reacted, according to Example 1, Method A, with 2.99 g. oxalic acid ethyl ester chloride (0.022 mol) in 60 ml. methylene chloride and 3.2 ml. pyridine. After recrystallisation from ethanol, there are obtained 5.0 g. (81.16% of theory) ethyl N - (4 - methoxy - 5,7 - dimethylbenzthiazol - 2 - yl) - oxamate; m.p. 143—144°C.

Mass spectrum: molecular weight found 308.

UV spectrum: λ_{max}: 308 mμ log ε 4.10.

The nuclear resonance spectrum (DDMSO) confirms the structure of the product.

Example 16

Ethyl N - (benzthiazol - 2 - yl) - oxamate.

4.5 g. (0.03 mol) of commercially available 2 - aminobenzthiazole is reacted, according to the procedure of Example 1, Method A, with 4.5 g. oxalic acid ethyl ester chloride. There are obtained 6.6 g. (88% of theory) ethyl N - (benzthiazol - 2 - yl) - oxamate; m.p. 187—188°C., after recrystallisation from ethanol. P. A. Petjunin describes this substance as a chemical intermediate with a melting point of 183—184.5°C. (Zh. Obshch. Khim., *34*, 28—34/1964).

Example 17

Ethyl N - (4 - methylbenzthiazol - 2 - yl) - oxamate.

a) Analogously to Example 8a) and b), using ammonium thiocyanate and benzoyl chloride, there is prepared 1 - (2 - methylphenyl) - thiourea; m.p. 158—159°C.

b) According to Example 8c), with the use of the Hugershoff reaction, there is prepared from the thiourea of Example 17a) (16.6 g.=0.1 mol), 2 - amino - 4 - methylbenzthiazole; yield 12.5 g. (76.21% of theory); m.p. 136—137°C.

c) According to Example 1, Method A, there are prepared from 4.9 g. (0.03 mol) of the aminobenzthiazole of Example 17b) by reaction with 4.5 g. (0.033 mol) oxalic acid ethyl ester chloride in 90 ml. methylene chloride and 4.8 ml. pyridine and usual working up, 7.4 g. (93.7% of theory) ethyl N - (4 - methylbenzthiazol - 2 - yl) - oxamate; m.p. 191—192°C. After recrystallisation from ethyl acetate, the melting point does not change.

IR: 5.74 and 5.86 (carbonyl).

Mass spectrum: molecular weight 264.

IV (methanol): λ_{max}: 309 mμ log ε 4.10.

Example 18

Ethyl N - (5,6 - dimethylbenzthiazol - 2 - yl) - oxamate.

17.8 g. (0.1 mol) commercially available 2 - amino - 5,6 - dimethylbenzthiazole is reacted, according to Example 1, Method A, with 15 g. (0.11 mol) oxalic acid ethyl ester chloride in 250 ml. methylene chloride and 16.1 ml. pyridine. There are obtained 23.3 g. (94.6% of theory) ethyl N - (5,6 - dimethylbenzthiazol - 2 - yl) - oxamate; m.p. 155—157°C. After recrystallisation from ethanol, the compound melts at 156.5—157°C.

Mass spectrum: molecular weight found 278.

UV spectrum: λ_{max}. (methanol) 316 mμ log ε 4.12.

IR: 1740 cm^{-1} (5.75 μ), 1705 cm^{-1} (5.87 μ).

Example 19

Ethyl N - (4 - chlorobenzthiazol - 2 - yl) - oxamate.

18.4 g. (0.1 mol) commercially available 2 - amino - 4 - chlorobenzthiazole is reacted, according to Example 1, Method A, with 15 g. (0.11 mol) oxalic acid ethyl ester chloride in 280 ml. methylene chloride and 16.1 ml. pyridine. There are obtained 23.3 g. (82.04% of theory) analytically pure ethyl N - (4 - chlorobenzthiazol - 2 - yl) - oxamate; m.p. 238—239°C. Recrystallisation from ethoxy - ethanol does not change the melting point.

Mass spectrum: molecular weight found 284.

IR: ester carbonyl 1732 cm^{-1} (5.77 μ)
amide carbonyl 1710 cm^{-1} (5.85 μ)

Example 20

Ethyl N - (7 - chloro - 4 - methoxybenzthiazol - 2 - yl) - oxamate.

a) According to Example 8a), 157.6 g. (1 mol) 2 - methoxy - 5 - chloroaniline are reacted with 145.1 g. benzoyl chloride and 78.3 g. ammonium thiocyanate in 1000 ml. acetone. There is obtained 1 - (2 - methoxy - 5 - chlorophenyl) - 3 - benzoylthiourea, which is further worked up as crude product.

b) The total still acetone moist N-benzoyl compound obtained according to Example 20a) is stirred into 2.8 litres 2N aqueous sodium hydroxide solution, heated under reflux for 10 minutes and hot filtered. The filtrate is subsequently cooled to 5°C. and the precipitate obtained is filtered off with suction, stirred with aqueous sodium bicarbonate solution and, after filtering, the solid product washed with water. There are obtained 1 - (2 - methoxy - 5 - chlorophenyl) - thiourea; m.p. 125—130°C. Yield 182.5 g. (84.23% of theory, referred to the chloroaniline used).

c) According to Example 8c), 108.4 g. of the thiourea prepared according to Example 20b) is reacted according to the Hugershoff method. As the first precipitate, there are obtained 46.4 g. (43.2% of theory) 2 - amino - 7 - chloro - 4 - methoxybenzthiazole; m.p. 200—203°C. From the mother liquor, there can be obtained a further 30—40% of the desired compound.

d) The 2 - aminobenzthiazole obtained according to Example 20c) is reacted in a 0.03 mol batch (6.44 g.) analogously to the procedure of Example 8d) or of Example 1, Method A. There is obtained ethyl N - (7 - chloro - 4 - methoxybenzthiazol - 2 - yl) - oxamate; m.p. 233—235°C. yield 70—80%.

Mass spectrum: molecular weight found 314.

UV spectrum: $\lambda_{max.}$ (methanol) 305 mμ log ε 4.08.

Example 21

Ethyl N - (5 - chloro - 4 - methoxybenzthiazol - 2 - yl) - oxamate.

a) 1 - (3 - Chloro - 2 - methoxyphenyl) - thiourea is prepared analogously to Example 8a) and b), *via* the N - benzoyl compound; m.p. 116—119°C. Total yield 90.53% of theory.

b) 2 - Amino - 5 - chloro - 4 - methoxybenzthiazole is obtained in 83% yield from the thiourea prepared according to Example 21a) by the Hugershoff method according to Example 8c); m.p. 185—187°C.

c) 10.73 g. (0.05 mol) of the 2 - aminobenzthiazole of Example 21b) are reacted with 7.5 g. (0.55 mol) oxalic acid ethyl ester chloride in 150 ml. methylene chloride and 8 ml. pyridine analogously to Example 8d) to give crude ethyl N - (5 - chloro - 4 - methoxybenzthiazol - 2 - yl) - oxamate which, after recrystallisation from ethanol, gives 13 g. (82.8% of theory) pure ethyl N - (5 - chloro - 4 - methoxybenzthiazol - 2 - yl) - oxamate; m.p. 186—187°C.

Mass spectrum: molecular weight found 314.

IR spectrum: 1694 cm^{-1} (5.90 μ) amide carbonyl.

Example 22

Ethyl N - (4 - chloro - 7 - methoxybenzthiazol - 2 - yl) - oxamate.

a) Analogously to the procedure described in Example 8a)—c), there are synthesised the following intermediates:

1) 1 - (2 - chloro - 5 - methoxyphenyl) - 3 - benzoylthiourea; m.p. 159—161°C. yield practically quantitative.
2) 1 - (2 - chloro - 5 - methoxyphenyl) - thiourea m.p. 168—170°C. yield 80.97% of theory
3) 2 - amino - 4 - chloro - 7 - methoxybenzthiazole m.p. 266—267°C. yield 92.16% of theory.

b) According to the procedure described in Example 1, Method A, 6.44 g. (0.03 mol) 2 - amino - 4 - chloro - 7 - methoxybenzthiazole are reacted with 4.5 g. (0.033 mol) oxalic acid ethyl ester chloride in 85 ml. methylene chloride and 4.8 ml. pyridine. There are obtained 8.7 g. (92.16% of theory) ethyl N - (4 - chloro - 7 - methoxybenzthiazol - 2 - yl) - oxamate; m.p. 266—267°C.

Mass spectrum: molecular weight found 314.

UV spectrum: $\lambda_{max.}$ (methanol) 300 mμ log ε 4.07.

IR spectrum: 5.78 μ; 5.85 μ ester and amide carbonyl.

Example 23

Ethyl N - (4 - trifluoromethylbenzthiazol - 2 - yl) - oxamate.

a) 2 - (Trifluoromethyl) - phenylthiourea is obtained, according to the procedure of Example 8a) and b), from 2 - trifluoromethylaniline in 81% yield; m.p. 158—160°C.

b) From the thiourea prepared according to Example 23a), there is obtained, by oxidative ring closure according to Example 8c), 2 - amino - 4 - trifluoromethylbenzthiazole; m.p. 149—151°C.

c) 4.36 g. (0.02 mol) 2 - amino - 4 - trifluoromethylbenzthiazole are reacted, according to Example 1, Method A, with 2.99 g. (0.022 mol) oxalic acid ethyl ester chloride. After recrystallisation from ethyl acetate, there are obtained 5.0 g. (78.6% of theory) ethyl N - (4 - trifluoromethylbenzthiazol - 2 - yl) - oxamate; m.p. 219—220°C.

Mass spectrum: molecular weight found 318.

UV spectrum: 317 mμ (methanol) log ε 4.16

IR spectrum: 3246 cm⁻¹ (3.08 μ) NH band; 1742 cm⁻¹ (5.74 μ), 1700 cm⁻¹ (5.88 μ) ester and amide carbonyl).

Example 24

Ethyl N - (6 - nitrobenzthiazol - 2 - yl) - oxamate.

5.85 g. (0.03 mol) commercially available 2 - amino - 6 - nitrobenzthiazole are reacted, according to the procedure of Example 1, Method A, with 4.5 g. (0.033 mol) oxalic acid ethyl ester chloride in 85 ml. methylene chloride and 4.8 ml. pyridine within the course of 45 minutes. There are obtained 7.7 g. (87% of theory) ethyl N - (6 - nitrobenzthiazol - 2 - yl) - oxamate; m.p. 253—254°C.

Mass spectrum: molecular weight found 295.

Example 25

Ethyl N - (4 - nitrobenzthiazol - 2 - yl) - oxamate.

a) 2 - Amino - 4 - nitrobenzthiazole is prepared, analogously to the procedure of H. Erlenmeyer and H. Ueberwasser (Helv. Chim. Acta, *23*, 328/1940) in 88% yield from 2 - nitrophenylthiourea; m.p. 263—265°C.

b) 5.85 g. (0.03 mol) 2 - amino - 4 - nitrobenzthiazole are reacted, according to Example 1, Method A, with 4.5 g. (0.033 mol) oxalic acid ethyl ester chloride in 85 ml. methylene chloride and 4.8 ml. pyridine within the course of 1.5 hours. The crude product obtained is freed from impurities by boiling with nitromethane. There are obtained 6.7 g. (75.7% of theory) ethyl N - (4 - nitrobenzthiazol - 2 - yl) - oxamate; m.p. 269—270°C.

Mass spectrum: molecular weight found 295.

IR spectrum: 3290 cm⁻¹ (3.04 μ) NH band, 1728 cm⁻¹ (5.79 μ), 1710 cm⁻¹ (5.85 μ) ester and amide carbonyl.

Example 26

Ethyl N - (4 - methoxy - 6 - nitrobenzthiazol - 2 - yl) - oxamate.

a) 2 - Amino - 4 - methoxy - 6 - nitrobenzthiazole is prepared according to the Kaufmann method as follows:

250 g. (1.49 mol) 2 - methoxy - 4 - nitroaniline are suspended in 440 ml. glacial acetic acid and mixed with 300 g. (3.1 mol) potassium thiocyanate. Subsequently, 237 g. bromine in 440 ml. glacial acetic acid are added dropwise at ambient temperature, with vigorous stirring, and stirring is continued for 72 hours at ambient temperature. Thereafter, the reaction mixture is diluted with 2.5 litres water and the precipitate obtained is filtered off with suction, stirred with a dilute aqueous solution of ammonia and again filtered off with suction. The precipitate is then washed with a copious amount of water, with a little ethanol and with some diethyl ether and then dried. The desired product is obtained in a yield of 282.6 g. (84.4% of theory); m.p. 260—265°C. It is sufficiently pure for further reaction.

b) According to Example 1, Method A, 6.75 g. (0.03 mol) of the 2 - aminobenzthiazole prepared according to Example 26a) are reacted with 4.5 g. (0.033 mol) oxalic acid ethyl ester chloride in 85 ml. methylene chloride and 4.83 ml. pyridine within the course of 30 minutes. The isolated crude product is boiled with 300 ml. ethanol and hot filtered. There are obtained 6.3 g. (64.94% of theory) ethyl N - (4 - methoxy - 6 - nitrobenzthiazol - 2 - yl) - oxamate; m.p. 270—271°C.

IR spectrum: 3270 cm⁻¹ (3.06 μ) NH band, 1700 cm⁻¹ (5.88 μ), 1710 cm⁻¹ (5.85 μ) double bonds, and 1728 cm⁻¹ (5.79 μ) amide and ester carbonyl.

UV spectrum: $\lambda_{max.}$: 364 mμ log ε 4.10.

The mass spectrum confirms the molecular weight of 325.

Example 27

Ethyl N - (1,3 - Dioxolo[4,5 - f]benzthiazol - 6 - yl) - oxamate.

a) 1 - (3,4 - Methylenedioxyphenyl) - 3 - benzoylthiourea is prepared analogously to Example 8a) from 3,4 - methylenedioxyaniline, ammonium thiocyanate and benzoyl chloride in 91.7% yield; m.p. 160—161°C. after recrystallisation from methanol.

b) 1 - (3,4 - Methylenedioxyphenyl) - thiourea is prepared from the N - benzoyl compound with sodium methylate in methanol according to Example 8b) in 76.53% yield, referred to the aniline compound used; m.p. 205—206°C.

c) From 14.7 g. (0.075 mol) of the thiourea of Example 27b), there is obtained by the Hugershoff reaction, analogously to Example 8c), by oxidative ring closure with bromine, 6 - amino - 1,3 - dioxolo [4,5 - f] - benzthiazole. Yield 12.4 g. (85.1% of theory); m.p. 228—229°C.

d) Analogously to Example 1, Method A, 5.8 g. (0.03 mol) of the benzthiazole of Example 27c) are reacted with 4.5 g. (0.033 mol) oxalic acid ethyl ester chloride within the course of an hour in 85 ml. methylene chloride and 4.83 ml. pyridine. The crude product obtained is recrystallised from nitromethane. The yield of pure ethyl N - (1,3 - dioxolo[4,5 - f]benzthiazol - 6 - yl) - oxamate is 7.1 g. (80.5% of theory); m.p. 241—242°C.

Example 28

N - (4 - Hydroxybenzthiazol - 2 - yl) - oxamic acid esters (mixture of methyl and ethyl esters).

5.6 g. (0.02 mol) of the ethyl N - (4 - methoxybenzthiazol - 2 - yl) - oxamate prepared according to Example 1, Method A, are

dissolved in 200 ml. chloroform, cooled to −20°C. and mixed within the course of 15 minutes with a solution of 10 g. (0.04 mol) boron tribromide in 50 ml. chloroform. Subsequently, the reaction mixture is allowed to warm up to ambient temperature. Then the same amount (3.78 ml.) of boron tribromide is added thereto at −10°C. and the reaction mixture subsequently stirred for 2 hours at ambient temperature. A further 0.01 mol boron tribromide completes the reaction. The reaction mixture is then mixed with methanol and the resultant precipitate filtered off with suction. There are obtained 5 g. of precipitate with a melting point of 205—212°C., which proves to be a mixture of the methyl ester with the ethyl ester of the desired oxamic acid, which mixture results by demethylation and simultaneous partial transesterification.

Mass spectrum: found 252 (methyl ester)
266 (ethyl ester).

Example 29

tert. - Butyl N - (6 - methoxybenzthiazol - 2 - yl) - oxamate.

26 g. (0.15 mol) Ethyl *tert.* - butyl oxalate (prepared according to the method of L. S. Carpino, J. Chem. Soc., *82*, 2725/1960) in 100 ml. xylene are heated to 100°C. and mixed with 18 g. 2 - amino - 6 - methoxybenzthiazole (0.1 mol). After stirring the reaction mixture for 8 hours at 100°C., it is cooled and filtered with suction. The residue is boiled with ethyl acetate and hot filtered. The precipitate obtained upon cooling is successively stirred with 2N hydrochloric acid and aqueous sodium carbonate solution. This residue is dissolved in methylene chloride, filtered and evaporated. The evaporation residue is triturated with diethyl ether and the resultant crystals filtered off with suction. There are obtained 8.1 g. *tert.* - butyl N - (6 - methoxybenzthiazol - 2 - yl) - oxamate; m.p. 230—232°C.

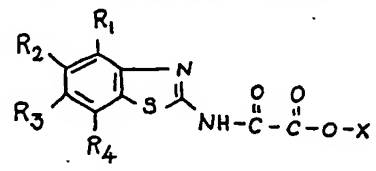
Example 30

Ethyl N - (6 - propoxybenzthiazol - 2 - yl) - oxamate.

5 g. 2 - Amino - 6 - propoxybenzthiazole are reacted with oxalic acid ethyl ester chloride in pyridine and methylene chloride in the manner described in Example 1, Method A. There are obtained 5.8 g. ethyl N - (6 - propoxybenzthiazol - 2 - yl) - oxamate (78% of theory); m.p. 143—145°C.

WHAT WE CLAIM IS:—

1. N - (Benzthiazol - 2 - yl) - oxamic acid derivatives of the general formula:—



wherein R_1, R_2, R_3 and R_4, which can be the same or different, are hydrogen or halogen atoms, hydroxyl or nitro groups, phenyl radicals, straight-chained or branched lower alkyl or alkoxy radicals or trifluoromethyl radicals or R_2 and R_3 together represent a methylenedioxy radical and X is a hydrogen atom or a lower alkyl radical, with the proviso that when X is an ethyl radical, R_1, R_2, R_3 and R_4 cannot all be hydrogen atoms; and the physiologically acceptable salts of those compounds in which X is a hydrogen atom.

2. Ethyl N - (4 - methoxybenzthiazol - 2 - yl) - oxamate.

3. N - (4 - Methoxybenzthiazol - 2 - yl) - oxamic acid and the sodium salt thereof.

4. Ethyl N - (6 - methoxybenzthiazol - 2 - yl) - oxamate.

5. N - (6 - Methoxybenzthiazol - 2 - yl) - oxamic acid.

6. Ethyl (6 - ethoxybenzthiazol - 2 - yl) - oxamate.

7. Ethyl N - (5 - methoxybenzthiazol - 2 - yl) - oxamate.

8. N - (5 - Methoxybenzthiazol - 2 - yl) - oxamic acid and the sodium salt thereof.

9. Ethyl N - (7 - isopropyl - 4 - methoxybenzthiazol - 2 - yl) - oxamate.

10. Ethyl N - (4 - methoxy - 7 - phenylbenzthiazol - 2 - yl) - oxamate.

11. Ethyl N - (7 - *tert.* - butyl - 4 - methoxybenzthiazol - 2 - yl) - oxamate.

12. Ethyl N - (4,7 - dimethoxybenzthiazol - 2 - yl) - oxamate.

13. Ethyl N - (5,6 - dimethoxybenzthiazol - 2 - yl) - oxamate.

14. Ethyl N - (4,6 - dimethoxybenzthiazol - 2 - yl) - oxamate.

15. Ethyl N - (6 - methoxy - 5,7 - dimethylbenzthiazol - 2 - yl) - oxamate.

16. Ethyl N - (4 - methoxy - 5,7 - dimethylbenzthiazol - 2 - yl) - oxamate.

17. Ethyl N - (4 - methylbenzthiazol - 2 - yl) - oxamate.

18. Ethyl N - (5,6 - dimethylbenzthiazol - 2 - yl) - oxamate.

19. Ethyl N - (4 - chlorobenzthiazol - 2 - yl) - oxamate.

20. Ethyl N - (7 - chloro - 4 - methoxybenzthiazol - 2 - yl) - oxamate.

21. Ethyl N - (5 - chloro - 4 - methoxybenzthiazol - 2 - yl) - oxamate.

22. Ethyl N - (4 - chloro - 7 - methoxybenzthiazol - 2 - yl) - oxamate.

23. Ethyl N - (4 - trifluoromethylbenzthiazol - 2 - yl) - oxamate.

24. Ethyl N - (6 - nitrobenzthiazol - 2 - yl) - oxamate.

25. Ethyl N - (4 - nitrobenzthiazol - 2 - yl) - oxamate.

26. Ethyl N - (4 - methoxy - 6 - nitrobenzthiazol - 2 - yl) - oxamate.

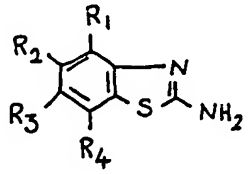
27. Ethyl N - (1,3 - dioxolo[4,5 - f]benzthiazol - 6 - yl) - oxamate.

28. Methyl and ethyl N - (4 - hydroxybenzthiazol - 2 - yl) - oxamate.

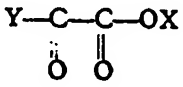
29. *tert.* - Butyl N - (6 - methoxybenzthiazol - 2 - yl) - oxamate.

30. Ethyl N - (6 - propoxybenzthiazol - 2 - yl) - oxamate.

31. Process for the preparation of N - (benzthiazol - 2 - yl) - oxamic acid derivatives of the general formula given in claim 1, wherein a 2 - aminobenzthiazole compound of the general formula:—



in which R_1, R_2, R_3 and R_4 have the same meanings as in claim 1, is reacted with an oxalic acid derivative of the general formula:—



in which X has the same meaning as in claim 1 and Y is a halogen atom or a lower alkoxy radical, or with a salt thereof.

32. Process according to claim 31, wherein, subsequent to the condensation reaction, at least one of the substituents R_1, R_2, R_3, R_4 and X is converted into a different substituent R_1, R_2, R_3, R_4 and X.

33. Process according to claim 31 or 32, wherein, when the product obtained is a salt, it is converted into a pharmacologically acceptable salt.

34. Process for the preparation of N - (benzthiazol - 2 - yl) - oxamic acid derivatives according to claim 1, substantially as hereinbefore described and exemplified.

35. N - (Benzthiazol - 2 - yl) - oxamic acid derivatives according to claim 1, whenever prepared by the process according to any of claims 31 to 34.

36. Pharmaceutical compositions, comprising at least one N - (benzthiazol - 2 - yl) - oxamic acid derivative according to claim 1, including ethyl N - (benzthiazol - 2 - yl) - oxamate, in admixture with a solid or liquid pharmaceutical diluent or carrier.

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